UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH



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TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES
ADVISORY COMMITTEE

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9th Meeting

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Thursday,

June 28, 2001

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The Advisory Committee was called to order at 8:30 a.m., in the Versailles Ballrooms I and II, of the Holiday Inn-Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland by Dr. David C. Bolton, presiding.

MEMBERS PRESENT:

DAVID BOLTON, Ph.D., Chairman

JOHN C. BAILAR, III, M.D., Ph.D.

ERMIAS D. BELAY, M.D.

DONALD S. BURKE, M.D.

DEAN O. CLIVER, Ph.D.

STEPHEN J. DEARMOND, M.D., Ph.D.

BRUCE M. EWENSTEIN, M.D., Ph.D.

MEMBERS PRESENT: (continued)

LISA A. FERGUSON, D.V.M.

PETER LURIE, M.D.

J. JEFFREY MCCULLOUGH, M.D.

PEDRO PICCARDO, M.D.

SUZETTE A. PRIOLA, Ph.D.

SHIRLEY JEAN WALKER

ELIZABETH S. WILLIAMS, D.V.M., Ph.D.

WILLIAM FREAS, Ph.D., Executive Secretary

GUESTS PRESENT:

RICHARD DAVEY, M.D.

DR. LOUIS KATZ, M.D.

DR. HARVEY KLEIN, M.D.

STEPHEN PETTEWAY, JR., M.D.

CONSULTANTS PRESENT:

PAUL R. MCCURDY, M.D.

KENRAD E. NELSON, M.D.

STANLEY B. PRUSINER, M.D.

# C O N T E N T S

PROCEEDINGS

(8:00 a.m.)

DR. FREAS: I would like to welcome everybody to this, our 9th meeting of the TSE Advisory Committee. I am Bill Freas, the Executive Secretary for the Committee, and both days of this meeting will be entirely open to the public.

At this time, I would like to go around to the head table and introduce those that are seated at the head table. Would the members and guests please raise their hand when I call out their name.

At the end of the table is Dr. Donald Burke, Director for the Center for Immunization Research, Johns Hopkins University.

The next chair is occupied by a standing member of this committee, Dr. Elizabeth Williams, Professor, Department of Veterinary Service, University of Wyoming.

Next is Dr. Jeffrey McCullough, a standing committee member, and he is a Professor in the Department of Laboratory Medicine and Pathology, University of Minnesota.

The next is an empty chair, which will soon be filled by Dr. Stan Prusiner, Professor of Neurology, University of California Institute of Neuro

Degenerative Diseases; and Dr. Prusiner will be a temporary voting member for this meeting today.

The next individual is a standing committee member, Dr. Peter Lurie, a medical researcher for the Public Citizen's Health Research Group, Washington, D.C.

And in the next chair is our consumer representative, Shirley Walker, Vice President of Health and Human Services, Dallas Urban League.

Next is a standing committee member, Dr. Dean Cliver, Professor, School of Veterinary Medicine, University of California at Davis.

Around the corner of the table is a new committee member, and I would like to welcome all our new committee members, the first one being Dr. Stephen DeArmond, Professor, Department of Pathology, University of California, San Francisco.

Next is another new committee member, Dr. Suzette Priola, Investigator, Laboratory of Persistent and Viral Diseases, Rocky Mountain Laboratories.

We will soon be joined in the empty chair by a temporary voting member for today, and he is Dr. Kenrad Nelson, and he is also Chairman of the FDA Blood Products Advisory Committee, and he is a Professor in the Department of Epidemiology, Johns

Hopkins University School of Hygiene and Public Health.

Next is the Chairman of this Committee, and he is Dr. David Bolton, head of the Laboratory of Molecular Structure and Function, New York State Institute for Basic Research.

Next is another new committee member, Dr. John Bailar, Professor Emeritus, Department of Health Studies, University of Chicago.

Next is a standing committee member, Dr. Ermias Belay, a medical Epidemiologist, Centers for Disease Control and Prevention.

Around the corner of the table is a standing committee member, Dr. Lisa Ferguson, Senior Staff Veterinarian, U.S. Department of Agriculture.

Next is Dr. Pedro Piccardo, Associate Professor, Indiana University Hospital; and next is a temporary voting member, Dr. Paul McCurdy, Consultant to the National Heart, Lung, and Blood Institute.

Next is a standing committee member, Dr. Bruce Ewenstein, Clinical Director, Hematology Division, Brigham and Women's Hospital of Harvard Medical School.

Next is a guest for today from industry, Dr. Stephen Petteway, Director of Pathogen Safety and

Research, Bayer Corporation.

Next is a guest, Dr. Richard Davey, and he is a representative from the Public Health Service Blood Safety and Availability Advisory Committee, in Washington, D.C.

Next is an invited guest, Dr. Lou Katz, Vice President for Medical Affairs and Medical Director for the Mississippi Valley Regional Blood Center, Davenport Iowa.

And at the end of the table is a guest, Dr. Harvey Klein, Chief, Department of Transfusion Medicine, National Institute of Health. Welcome to everybody.

Dr. Pierluigi Gambetti is a new member of this committee who could not be with us today. I would now like to read into the open public record the conflict of interest statement for this meeting.

The following announcement is made part of the public record to preclude even the appearance of a conflict of interest at this meeting. Pursuant to the authority granted under the committee charter, the Director for the Center for Biologics Evaluation and Research has appointed Drs. Paul McCurdy, Kenrad Nelson, and Stanley Prusiner, as temporary voting members for the meeting.

Dr. Lester Crawford has been appointed as a temporary voting member for tomorrow's session. Based on the agenda made available, it is has been determined that the agenda addresses general matters only.

General matters waivers have been approved by the Agency for all members of the TSEAC Advisory Committee, as well as consultants for this meeting.

The general nature of the matters to be discussed by the committee will not have a unique and distinct effect on any members' personal or imputed financial interests.

In regards to FDA's invited guests, the Agency has determined that the services of these guests are essential. The following reported interests are being made public to allow meeting participants to objectively evaluate any presentation, and/or comments made by the participants.

Dr. Richard Davey is employed by the Georgetown University. He is also a member of the PHS Blood Safety and Availability Advisory Committee.

Dr. Christl Donnelly consulted with Oxford Biologica. Dr. Lou Katz is employed by the Mississippi Valley Regional Blood Center. Dr. Harvey Klein is employed by the Department of Transfusion

Medicine, National Institute of Health.

Dr. Stephen Petteway is employed by the Pharmaceutical Division of Bayer, and consults with Intersouth Investors, and is an advisor for Biologic Science Board.

Dr. Robert Rohwer consults widely on TSE issues with both blood industry and gelatin industry, for which he receives compensation. His laboratory research program receives support from the Gelatin Manufactures of Europe. Dr. Rohwer is an advisor and has equity positions in several companies related to TSE.

Dr. Michel Schoentjes is employed by SKW Gelatin and Specialties, France. He also is the vice president of the Gelatin Manufacturers of Europe. Dr. Jean-Hugues Trouvin is employed by the Department of Biologics, France.

In addition, listed on the agenda are speakers making industry presentations. These speakers were not screened for conflict of interests because they are employed by industry, and are invited here to present industry's point of view on this topic.

In the event that the discussions involves specific products or specific firms for which FDA's

participants have a financial interest, or participants are aware of the need to exclude themselves from such involvement, then their exclusion shall be noted on the public record.

A record of waivers are available upon written request under the Freedom of Information Act. With respect to all meeting participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they wish to comment upon.

Dr. Bolton, I turn the meeting over to you.

CHAIRMAN BOLTON: Thank you, Bill. I won't say much this morning in my opening remarks as we have a very full agenda. I want to do a couple of things. I want to welcome the new members of the committee.

We are very happy as I am sure the FDA are very happy that you have agreed to serve on this committee. I consider and have for the last few years a privilege to serve as a member of the committee, and now I am doubly honored to serve as the Chairman of the Committee, although you may have to check back with me this evening to see if I am still in that mood.

I would also like to thank the returning

members of the committee for their continued service. I think it is a very important thing that you do, and you have done it, and know how difficult it can be at times.

We do provide an important service both for the FDA and obviously for the nation at large, in trying to help them come to an understanding of some very difficult issues, and often times with very little information, and not as much as we would like to have, but as much as is available.

And I guess with that, I think we will move on to the first topic of the day, which is -- oh, and I have one more thing actually. I want to thank also the former members of the committee who are now serving as consultants, and in particular, Stan Prusiner, my former mentor.

And I have the gavel, and so I have an opportunity now to overrule.

DR. PRUSINER: Couldn't we read something into the record.

CHAIRMAN BOLTON: And that is another thing. Those who are returning members of the committee recall our usual set-up with the microphones that have switches on them.

I think that these may be live all the time.

So just be aware that you may have a live microphone sitting in front of you.

DR. FREAS: Could I just comment on that? The microphone is turned down right now. So if you start talking, the microphone may not be very loud. But please don't put down this microphone, and try to pick up a microphone next to you.

Keep talking and the gentleman at the sound board will then turn up the volume. But, please, your microphone should be working. Just pause a little bit until the volume has been turned up.

CHAIRMAN BOLTON: Okay. Well, the first topic for this morning is topic one, the suitability of blood donors who have lived or traveled in various countries based on recent information concerning new-variant Creutzfeldt-Jakob disease, and bovine spongiform encephalopathy.

And our first presentation will be the introduction, charge, and questions by Dr. David Asher of the FDA.

DR. ASHER: Thank you, David. Good morning. Today we are asking the committee to review for the third time the issue of blood donors potentially exposed to the BSE agent, and hence having some probability, presumably very small, of incubating

Creutzfeldt-Jakob disease.

There is a theoretical risk that their blood might serve as a vehicle to transmit the effects to recipients. The FDA has already recommended a limited deferral policy for some potentially exposed donors, and the committee previously advised a modest extension of that policy.

Much less is known about variant Creutzfeldt-Jakob disease in other forms. As you may recall, unlike sporadic vCJD and variance CJD, the abnormal protease-resistant prion protein accumulates to substantial levels of lumpohoid tissues, and of course some lymphoid cells normally enter blood.

That raised a concern early on that the relatively reassuring epidemiological evidence suggesting that blood was unlikely to be an important vector for other forms of CJD might not be predictive for variance CJD.

Then came reports last year that BSE had been transmitted by blood of experimentally infected mice, and finding that not uncommon in other rodent TSC models; and then by transfusion from an experimentally infected sheep, a unique isolated and preliminary finding, but one that is troubling nonetheless.

Rates of variant CJD have continued to rise in the U.K., although fortunately not in France. Two other cases have been reliably diagnosed outside the U.K. and France, but both were in long-time U.K. residents.

Attempts to transmit TSE to mice and monkeys from blood of patients with variant CJD have apparently been negative, but the total volume of blood tested has been small.

A number of recipients are said to remain well after receiving blood products from donors who later went on to get variant CJD, but they have been observed for only a few years. We may hear more about that in this afternoon's session.

Concern about the potential infectivity of blood from persons incubating variant CJD prompted FDA's current precautionary policy announced in 1999 for implementation by April of last year.

That policy recommends deferral of donors residented in the U.K. for any cumulative six months from the presumed start of the BSE epidemic in 1980, to the full implementation there of a series of measures to prevent human exposure to the BSE agent implemented by the end of 1996.

Since there is no early diagnostic test to

Now there is concern not only about donors exposed to BSE in the U.K., where cases of variant CJD continue to rise to 104 at my last count, but also about people who ate U.K. beef products in continental European countries.

The three French patients with variant CJD had no history of travel to the U.K. France may have imported at least five percent of its supply of beef products from the U.K. during some years of the epidemic. So there were ample opportunities for exposure there.

Other European countries also imported U.K. beef. There is also concern about the spread of BSE into other national cattle herds because U.K. meat-and-bone meal was exported to many countries, and possibly used in cattle feed.

In just the last year, four new European countries have recognized BSE in native cattle. So BSE may have spread more widely in European cattle than previously thought.

Now there is in addition to the risk from U.K. beef an additional risk to humans from indigenous BSE in cattle of continental Europe. Regarding variant CJD itself, there is both bad news and good news.

identify donors who will get variant CJD, and no validated screening test to identify blood bearing the infectious agent, the deferral of donors offers the only practical way to reduce the theoretical risk.

The current policy was predicted to remove almost 87 percent of total risk expressed as donor days in the U.K., while deferring 2.2 percent of donors, which is a substantial number.

No appreciable loss of donors was observed after implementation, and no methods for monitoring donor losses are not well developed.

This committee reviewed the situation on January 18th of this year, and offered the FDA seven pieces of advice summarized in this slide, taking some liberties in the interest of clarity.

First, continue to defer donors who spent any cumulative six months in the U.K. from 1980 through 1996. Defer for 10 years residence in France from 1980 through the present, but recommend no blanket deferral for other European countries.

By the narrowest of margins, the committee did advise deferring donors who spent 10 years in Portugal, or the Republic of Ireland, from 1980 to the present.

The committee also advised not adding up the

total time donors have spent in different BSE countries to determine deferral, and not treating exposure to U.K. beef on U.S. military bases as being equivalent to exposure in the U.K., although some deferral policy not further specified for donors exposed to U.K. beef on Department of Defense bases was advised.

The FDA acknowledges the concerns that the committee expressed in January, agreeing that the risk of transmission of variant CJD is theoretical, and that the potential loss of blood donors from increased deferrals is substantial.

The FDA also understands the reluctance of the committee to lump together under one deferral policy all 30 countries, that in addition to the U.K., are under the current U.S.D.A. BSE list.

However, the FDA has not been convinced that existing information is adequate to justify recommending a stratified risk-based policy for deferral of donors potentially exposed to the BSE agent in France, Portugal, and Ireland, while accepting the risk of exposure in other continental European countries.

The vast majority of BSE cases is more than 180,000 have been diagnosed in the U.K. Britain

reported 1,352 cases for the year 2000, and 177 through the end of April of this year.

Although Ireland and Portugal indeed have the next highest numbers, 613 and 568 cases to date, according to OIE figures earlier this month, BSE cases in Switzerland were also substantial, exceeding the number reported from France.

The numbers of BSE cases in cattle borne in Germany and Spain to date seem more modest, 75 and 46. But it is troubling that all of those cases were found just within the past 10 months, and one additional country, the Czech Republic, confirmed its first case of BSE only two weeks ago.

Considering the uncertainties surrounding the prevalence of BSE in Europe, the FDA staff doubt the ability of available risk assessments to provide reliable estimates of potential human exposure to BSE agent in various countries. Drs. Kreysa, and Trouvin, and Donnelly may elaborate on the situation later in the morning.

So it is difficult for the FDA to be confident that a bright line can be drawn distinguishing the risks of human exposures to the BSE agent in France, Ireland, and Portugal from risks elsewhere in Europe.

There seems to be consensus among stakeholders that until the potential infectivity of blood from persons incubating variant CJD is better understood, and we all hope that it will eventually prove not infectious, deferral of those donors with the greatest probability of past exposure to the BSE agent is prudent.

Most of us also agree that it will not be feasible to defer all donors who spent any time in a BSE country, but that the risk can be greatly reduced, but not completely eliminated by a donor deferral policy.

Furthermore, everyone is committed to providing an adequate supply of safe blood to all persons who need it. But the potential loss of blood donors that might result from additional deferrals to be considered today are very large. Two of them are probably without precedent.

It is clear that any substantial loss of additional blood donors, if not compensated by greatly increased efforts to recruit suitable new donors and retain them, would inevitably cause shortages and almost certainly hurt some people needing blood products to sustain life and health, an unacceptable outcome.

Unfortunately, the uncertain state of knowledge about BSE and variant CJD does not yet allow us to develop a policy that is strictly science-based, and as I think we will learn during our open public hearing today, there is no consensus among stakeholders either about the probable magnitude of the BSE risk, or the additional deferrals that blood programs can safety tolerate.

With those things in mind, we ask the committee to review four options for additional deferrals; a slightly modified version of the policy they advised in January; an aggressive policy recently proposed by the American Red Cross; a compromise option developed by the FDA; or any other program that committee members or representatives of blood programs or others may propose.

The FDA intends to use the committee's advice to develop a revision of the current guidance for industry to be published as a proposal for comment, a proposed revision, so that everyone concerned will have another chance to provide additional information, identify problems, and suggest solutions to the FDA.

And I might add here that we are prepared to receive additional comments at any time after today's

meeting before the issuance of the proposed guidance.

We anticipate that after analysis of comments a final guidance we will then issue for implementation within six months of issuance. We also encourage well-planned and monitored pilot studies, using deferral options that exceed FDA policies. By the way, additional background information is available through the CBER website.

Helping us today are several expert speakers. Dr. Joachim Kreysa led the European commission's scientific steering committe's group that developed the geographic BSE risk analysis, a qualitative assessment of the risk and possible prevalence of BSE in countries responding to a request for information.

Professor Jean-Hugues Trouvin, of the French Blood Services, will provide another view of the situation concerning BSE in blood from the European medical perspective; and Christl Donnelly will present the results of epidemiological models to assess risk of human infection with the BSE agent in several countries, perhaps providing a paradine for assessments of risks in other places.

Dr. Tony Giulivi from the Canadian Blood Services will share the results of important risk

assessments performed in Ottawa, and we have also asked Tony to consider the effects on public health that might be expected should shortages of various magnitudes occur.

Then FDA's Alan Williams will describe a model that he developed to estimate reductions in risk offered by various deferral options, as well as losses of donors that might be expected based on a survey that he coordinated. He will also expand on the advantages an disadvantages of each option.

It is especially important to remember that predicted donor losses would not be borne uniformly across the USA. Losses will be more severe in the metropolitan areas of the East and West Coast, and especially in the New York City area.

Several speakers in the open public hearing will undoubtedly address that problem. The committee will then be asked to discuss the options, and then finally to vote on them.

In your discussions, we ask members to consider reductions in risk and donor losses predicted from the model, because that provides a useful way in which to compare options.

Dr. Williams will describe the model fully, but it may be useful now to list some of its

underlying assumptions. The risk of human infection is assumed to be proportional to the duration of exposure and to the fraction of consumed beef likely to have been contaminated.

And food chain protections are assumed to be substantially effective in reducing exposure so long as they are faithfully implemented. The risk is taken to have been greatest in the U.K.

The Department of Defense risk is taken to have had a maximum of 35 percent U.K. risk, and risk in France, 5 percent, and risk in the rest of Europe extrapolating from Switzerland, 1.5 percent of U.K. risk.

Now to summarize features of the options briefly. Option 1, based on the committee's advice of January, proposes to defer donors who spent six months or more in the U.K. from the beginning of 1980 through the end of 1996, which is FDA's current policy.

Or six months or more on a DoD base from 1980 through 1996, or open through 1990 on bases north of the Alps; rr 10 years or more in France or Portugal, or Ireland, from 1980 to the present. This option is estimated from the model to yield a total reduction in exposure risk of 82 percent at a cost of 2.2 percent of current dollars.

The American Red Cross proposal, Option 2, is to defer donors who spent any period of three months or more in the U.K. from 1980 to the present, or six months or more in the rest of Europe in the same years, as well as any recipient of blood transfusion in the U.K. from 1980 onwards.

Reduction in total donor BSE exposure risk is estimated by the model to be about 92 percent, and donor loss from 7.8 to 9.1 percent. The range of results from survey donors who reported travel to both the U.K. and other European countries, Alan can explain that later.

The FDA's compromise proposal, Option 3, would defer donors resident for any period of three months or more in the U.K. from 1980 through 1996, or for six months or more on a Department of Defense base from 1980 through 1996, or only through 1990 on those bases north of the Alps.

Or for five years or more in the rest of Europe from 1980 through the present, as well as any recipient of a blood transfusion in the U.K. from 1980 until the present.

The reduction in total donor BSE exposure risk is estimated to be about 91 percent, and donor loss from 4.6 to 5.3 percent, which is still a one-

time loss of donors that would be unprecedented I am told in the history of U.S. blood banking.

Of course, if the American Red Cross implements its proposed policy, the national donor loss would be greater than indicated both for options one, and for this option depending on the number of blood programs that elected to follow the American Red Cross. In that case the risk reduction would also be significantly greater under Option One.

Here now are the questions that the committee will be asked. The first three are accompanied by a review of the summaries of the relevant options to it to assist you.

We will ask the committee to vote on the FDA proposal first by answering question one. Do committee members concur with the FDA proposal, and that is Option 3 that we just summarized, to defer additional blood and plasma donors based on their potential exposure to the agent of BSE.

If the committee does not endorse the FDA proposal, we will ask you next to answer Question 2. If they do not agree with the option proposed by the FDA, do committee members advise the FDA to recommend a blood and plasma donor deferral policy recently proposed by the American Red Cross, and that is Option

2.

If the committee also declines to accept the American Red Cross proposal, then in Question 3, we will ask them to consider the option based on the committee's earlier advice in January of this year.

If they do not agree with the previous options, do TSC advisory committee members advise the FDA to recommend a blood and plasma donor deferral policy based on advice by the committee on January 18th, 2001, and that is Option 1.

Then if none of the three options has been endorsed, then in Question 4, we will ask the committee to suggest or accept some other option.

Finally, after the committee has voted on the options, in Question 5, we will ask them to comment on steps that should be taken to monitor and ensure adequate national and regional supplies of blood, blood components, and plasma derivatives, if additional donors are deferred based on possible exposures to the BSE agent.

We look forward to having an informative session this morning, and I thank you very much.

CHAIRMAN BOLTON: Thank you, David. We are running a little ahead of schedule actually, and so at this point in time, I would just like to ask any of

the committee members if they have any questions for David on these proposals. Yes?

DR. LURIE: David, my question is that it is not my recollection that previous guidances that have ensued from our committee suggestions have resulted or have been produced in a notice and comment period, and so forth, and so on. Am I correct about this?

My concern is that -- I mean, there have been now three at least advisory committee meetings on this, with the industries being given ample opportunity for input, including again today. So I am wondering if this is an unusual procedure at all.

DR. ASHER: I can't comment on whether it is absolutely unusual. The last version of the guidance for blood donors potentially at increased risk of CJD was issued as a draft guidance I believe in the summer of 1999, and only in final form in November. So that there was an opportunity for comment.

As I recall, the gelatin guidance in 1997 was issued without opportunity for notice and comment, although there was an active, though public, discussion at a TSC advisory committee meeting.

DR. PRUSINER: David, I wonder if it wouldn't be useful for you to review the FDA's position and why it chose 1996 as that cutoff, because

when we had these discussions originally, it may be my failed memory, but I never remembered a cutoff date.

You all talked about beginning this in 1980 and looked at that very carefully, and then these epidemiologic studies were done every six months to look at donor loss. But I would like to hear from you why the FDA then decided that 1996 was the cutoff date.

DR. ASHER: The decision was made in response to information provided by the U.K. about when there had been full implementation of the food chain protections, and those are removal of specified risk materials over a 30 month slaughter scheme, and the prohibition of advanced meat recovery.

I wasn't part of the discussions that chose that date, and perhaps Dr. Epstein, who was, would want to comment further on the considerations that went in to selecting the end of 1996 for the cutoff.

DR. EPSTEIN: That issue was a part of the discussion, and you have already given the answer. The concept was that the food chain protections had been sufficient by that time, and we did hear an estimate for the number of infected animals that could potentially enter the food chain subsequent to that date.

It was felt to be less than one per annum, and so it was on that basis that we made that decision, but it was a discussed issue back in 1998-1999.

DR. PRUSINER: It was or was not?

DR. EPSTEIN: It was discussed.

DR. PRUSINER: So my memory is failing.

DR. EPSTEIN: However, with respect to deferral for exposure in Europe, we have asked the committee both in June of 2000 and January of 2001 whether there should be such a deferral, and we basically proposed a 10 year exposure period leading to deferral, and in that case we did not put a limit on it because we felt that we did not have knowledge when food chain safeguards throughout Europe were adequate, if indeed they are at all.

DR. ASHER: You may notice the deferral for injection of bovine insulin from the U.K. was also not part of the discussion. The agency does have discretion to go beyond the committee discussion.

DR. PRUSINER: I'm not challenging that. I was just asking.

DR. ASHER: And those are my understanding for why that happened. By the way, if anyone feels that the cutoff date is '96 is not appropriate, this

would be a useful venue in which to discuss it.

DR. PRUSINER: I just think that is very important, David, that as the Chair for you to bring that up, and that we discuss this issue of 1996 later.

CHAIRMAN BOLTON: Steve, you had a comment or a question?

DR. DE ARMOND: So when I look at your tables here, particularly this table of kind of comparing risks and the effect on blood donor loss, the only other issue that I don't understand and would like to see some data on, or some calculation on, is the risk of deaths due to the decrease in the blood supply.

We are talking about a theoretical risk in terms of BSE to variant CJD, to humans receiving blood supplies. But we don't understand, or at least I don't understand what a decrease of 5 percent, 8 percent, 9 percent, would mean in terms of real deaths.

DR. ASHER: Yes. Tony Giulivi is going to be presenting a graphic prediction of what various -- of what donor losses of various magnitudes would mean for public health, and it answers exactly that question.

And of course there is going to be a full

discussion of the model by Alan Williams later in the morning.

CHAIRMAN BOLTON: Dr. Cliver.

DR. CLIVER: What I am disappointed not to have seen is any broader trace of where British beef and British beef bone meal went during the suspect period. What we are seeing now is a kind of ethnocentric focus on Europe, and we don't know how much of those products went to Asia and Africa.

Over half of the world's population lives on those continents, and the idea that my visiting in Europe puts me at risk, but perhaps eating some things on another continent doesn't put me at risk, I would like to see some documentation to that.

DR. ASHER: Well, unfortunately, the documentation concerning the export of meat and bone meal from the U.K. is limited. U.K. customs and Excise has, I believe, published a list of exports.

The problem is that they don't match very well with the country's own records of imports, and there has apparently been a lot of -- for instance, there was importing of a certain amount of British beef and bone meal into the United States that apparently doesn't match our customs records for import.

So I don't pretend to be an expert on either topic. The Ministry of Agriculture, Fisheries, and Foods was quick to point out the reliability of their own records is really questionable.

So it is complicated by inaccurate records in the U.K., or incomplete records in the U.K., and accurate records or incomplete records in the importing country, and the probability that there was a considerable amount of untraced transhipment from one country to another.

But I think that your concern is very well taken. We are all concerned about the possibility that BSE was exported to many countries around the world.

At the moment, the FDA has found the only realistic way in the absence of independent sources of information that we can function in a practical sense is by relying on the U.S. Department of Agriculture's determination of which countries are at high risk of having BSE in their cattle.

And you will hear more about that from Dr. Kreysa from the European Commission's independent and thorough efforts to determine the risk in the various countries.

Those efforts are also limited by the fact

that the countries self-report and not every country has sent a dossier in to the scientific steering committee.

CHAIRMAN BOLTON: Thank you, David. One more?

DR. FERGUSON: Actually, let me add just a bit to David's response to the last question. I am speaking for USDA and then also two hopefully quick questions just for clarity's sake.

The Department is in the process of trying to obtain information to allow us to assess the risk of countries, especially in Asia, based on all the recent concerns.

We just recently started that process, and as David said, that is obviously dependent on those countries reporting to us. But we have started that process, and so hopefully we will have some more of that information available to us here in the next few months.

Two questions for clarity's sake. How are you defining European country? Is that the same as ours? Is it the USDA list? And then also what is the distinction in the DoD bases, and why the difference between those bases north of the Alps?

DR. ASHER: First, the European countries on

the list, we were intentionally vague about Europe because frankly we anticipate that the USDA will perhaps soon expand the -- that the line that the USDA has drawn in Europe at the moment is at the border of the former Soviet Union, which has a history of -- at least according to British Customs and Excise records, a history of importing meat and bone meal from the U.K.

Now, where that meat and bone meal went inside the former Soviet Union, we do not know. But we anticipate that additional European countries not currently on the USDA BSE list will in all probability be appearing on that list before too long. Am I correct in that assumption?

As much as possible, we would like to rely on the USDA list, but the actual issuing of interim guidance, in which the interim regulation in which the USDA promulgates its list, it lags somewhat behind the appreciation of risk. The other question was?

DR. FERGUSON: The distinction on the DoD based north of the Alps and the time frame.

DR. ASHER: Colonel Fitzpatrick is here today. The program purchasing U.K. beef for European military bases north of the Alps stopped in 1990, and continued in bases south of the Alps, and there is a

list of what constitutes a base north and south of the Alps.

It continued until 1996 south of the Alps. And, of course, 35 percent is thought to have been the maximum percentage of U.K. beef that was purchased for any base, on many bases, and presumably the amount of beef purchased from the U.K. was less than that.

CHAIRMAN BOLTON: Okay. So I would like to just remind the committee how we are going to deal with this. Once we get to the public comment and our discussions, we will actually be voting on these proposals sort of out of order.

We will first discuss and vote on the FDA plan, and then the American Red Cross plan, and then finally the committee's recommendation from January 2001.

And so if you are uncomfortable with some part or disagree with some part of each of those proposals, you can always vote no on each of them, and if we vote no on all of them, then the fourth item is do we have a new recommendation that we would like to consider.

So as you listen to the proposals this morning, keep those in mind. This is a lot of information to juggle about in one's brain, and we are

looking at competing risks.

I think as Dr. DeArmond pointed out, a real risk of a shortage in the blood supply, versus some theoretical risk of transmission of new variant CJD are numbers that we don't really know much about.

So having said that, we will move on to our first informational presentation, and that is the -- sorry.

DR. BURKE: Will there be an opportunity for the Red Cross to present their position, and is the FDA or someone going to present for them, and do we know what their positions are, and whether or not they accept the FDA's estimates, and the rationale for their proposed policy change?

CHAIRMAN BOLTON: Yes, I believe that they are on the open public hearing today as presenters. And we certainly -- I hope to provide adequate time for discussion of all of these various points of view.

The problem that we may run into is that I would also like to keep this session intact if at all possible, and that may mean that we would push lunch back beyond the 12:45 time at this point.

But if it gets to the point that we are not able to wrap up discussion, we may have to break for lunch first, and then come back and continue the

discussion and vote. So keep that in mind also. Okay. So any more questions?

(No audible response.)

CHAIRMAN BOLTON: Good. Oh, I would like to remind everybody on the committee, too, that it may be helpful for the transcriber if you give your name before -- oh, it is not necessary? Very good.

All right. Our first presentation this morning is by Joachim Kreysa. It is the geographic BSE risk assessment conducted for the European Commission. Dr. Kreysa.

DR. KREYSA: Chairman, Ladies and Gentlemen, first of all, thank you very much for this opportunity to speak to you on this geographic BSE risk assessment, which has been carried out over the last three years by the scientific steering committee.

I am one of the two secretaries of this committee and have been monitoring this event since the beginning.

I will speak about the method and the results, but following a request from Dr. Asher, I will also speak a little bit about risk management, and the BSE risk management issues or measures which have been talked about in Europe, which will also clarify a little bit the changes in the possible risk

for humans over time in the European Union.

The staffing point of this is obviously the BSE transmission to humans, and that is the reason why everybody is so concerned about it. Up to now the mechanisms are not fully understood as far as I gather from the discussions of our committee.

The most likely of this is the exposure via food, and finally you run the risk of exposure of man to the agent is dependent upon manufacturers, but first of all on the risks that the agent enters the food chain and came into the human plate.

The BSE assessment is an attempt to estimate the risks in a given country or region the lines could be incubating BSE. At the moment, there are in fact no cases already recognized.

So GBR is not very essential anymore when you want to assess the prevalence in a country that you know already that BSE is there, but it is useful to see if there is a risk of BSE in a country which has not yet found its first case.

The GBR is not an assessment of the human exposures. It is based, however, on the currently available knowledge about the BSE agent, its transmission, the pathogenesis of the disease, and the possibility to control its propagation.

It is on the other hand also flexible enough to take account of new information of the uncertainties that still exist, which means that the method is so simple and crude that we can easily adapt it, but that we also only provide qualitative science.

If we go into the question of the knowledge, the first question which is always raised is the question of the origin of BSE. There are many hypotheses, such as spontaneous occurrence, which was never proven; or the effective scrapie moved into bovines, which up to now has not been experimentally shown.

But it is nevertheless one of the most favorite hypotheses. For the purposes of GBR, the EC simply assumes that BSE exists somehow and we don't know exactly yet how in the U.K.

It was distributed from the U.K. and later on from other countries which developed the BSE in their own national health via the export of feedstuffs and of infected cattle. Apparently, there are also other products which could have exported it, but these are the most important ones.

The next element is to have an idea on the transmission system for BSE, and it is very clear that horizontal transmission seems simply not to happen,

and the transmission from cattle to cattle has not been discovered.

The question of vertical transmission is also an open one, and it has been stated, but it has not been shown finally, and particularly the biological mechanism is not understood.

Then we have the clear transmission root of the oral transmission via feed, which in fact is the one that seems to be non-disputed. And then we have discussions on the transmission via semen, embryos, or also other third routes, but not of these has yet really shown a remarkable effect. So for the GBR, in fact, we are only on the oral route.

The next big aspect which as already been mentioned this morning is the question of what happens with the BSE once it is in a country, and if the transmission route is feed, there must be a recycling from the live animal back to the live animal via the feed chain.

And in fact that is the basic thought of the BSE model. With BSE infected cattle in a country, these cattle are going to be processed at a certain point in time, which means that infected BSE, or infected BSE infective materials are rendered into feed.

And domestic MBM infected cattle, and cattle are exposed, and the vicious circle is closed. So a question which has to be addressed is this vicious circle existing or not in a country. Fortunately, this feed back loop can be controlled.

And now the first one which is always the first element or control point of ordinary services is surveillance, and to a certain extent, culling. Culling means the slaughtering of cattle which are perceived to be at risk of incubating BSE because of the link to an index case.

The next element or control point would be to exclude SRMs. SRMs are these famous specified risk materials which according to the SSC would contain something like 95 or 98 percent of infectivity in a material BSE case.

Excluding these obviously reduces the amount of infectivity entering, and rendering, and therefore reduces the risk in their system. The same is not the same, also quite interesting, is the age at slaughter.

Because of the long incubation period and the ideas that we have about the development and the building up of infectivity in the bodies of the cattle, the other animals are generally at much later risk, even older animals, simply because even if they

are infected at birth, or close to birth, they will have had not enough time to build up a lot of infectivity.

Very often they will have even have reached the brain and the spiral cord measurable radius. The rendering process and the feeding and feed controls are obviously also very important steps.

Rendering processes can reduce if properly applied the infectivity of the material by a factor of about three logs. So by a factor of a thousand. The SSC insists, however, to make clear that they cannot sterilize.

So if a lot of infectivity enters rendering the upcoming MBM is not to be regarded as safe. This has been shown by countries who rely too much on this one control.

The feeding is obviously one of the cull or key factors to control. If you can avoid cattle with receiving MBM, or contaminated MBM to be very precise, ruminant MBM, you would break the cycle, and the vicious circle would not work.

The problem there is the control of the cross-contamination. The European experience shows that whenever you are feeding it to other animals, you have a risk of cross-contamination, and this is

difficult to control.

However, to start the whole thing rolling, you need an initial source of BSE, and according to the GBR model, this is imports on the one hand, and it is the import of MBM, which would lead to exposure of cattle to the BSE agent.

Apparently measures which are controlling the fate of the imported MBM in the country can manage this does make sense. Then we have the import of cattle, which would increase the number of BSE infected cattle in the country.

Again, surveillance of these imported cattle could manage that risk; and we have seen in our GBR exercise examples of those countries who control the import of MBM, and in particular of cattle, so that they have imports, but these cattle did not reach internal impact routes.

So the GBR exercise, on the basis of this model and these thoughts, simply tries to answer two main questions. First, is the risk to the BSE agent important, and this is difficult enough.

We have just heard about the problematics with the U.K. export figures to compare the disease import figures, and what we do is we have very intensive discussions with the country of these

figures, and we try to verify this by all means, even by going back to the importing and exporting countries, requesting a very detailed research on that.

The second question is, yes, what would have happened on the one hand if BSE was recycled and probably amplified, or was it eliminated? And this obviously depends on the internal system.

The recite of this is in the Geographic BSE Risk, which is a qualitative indicator of the likelihood that one or more cattle are present in a country or region while being infected with the BSE agent clinically or pre-clinically.

The SSC defines four levels which are I guess readily well known. Number One says that it is highly unlikely that the BSE agent is present. The second one is that it is unlikely, but it cannot be excluded, that the BSE agent is present.

Third, it is likely that the BSE agent is present or confirmed at the lower level; and this lower level simply means that a lower arbitrary level was taken of less than a hundred cases per million adult cattle confirmed in the last 12 months.

This is just in line with the OIE, the international standards setting organization, and then

we have finally the last two, and we have only two countries that come from the higher level, and that means more than a hundred cases per million of adult cattle.

When the SSC produced these four levels, it had in mind the ultimate objective, which is the contribution to the managing of the risk for humans. So these levels should give risk managers a kind of orientation of what should be done.

And under this perspective, level one would means nothing is needed to be done. Secondly, the second level would be that some precautions should be taken, and this can vary depending on the specific situation of the country.

And level three would mean that precaution measures must be taken, because there is a real risk that BSE infected cattle exist in the country, and therefore infectivity could end up in the domestic line of the food chain.

And in the mind of the SSC, for example, SRM in feed ban should be there, and there should be good rendering in the country, and an active surveillance and cohort culling should be in place to really estimate as good as possible the risk.

And then level four apparently everything

must be taken that can be conceived to reduce the risk of human exposure to the agent, and in our view this is successfully done in the U.K., where the human exposures might be very low.

The current GBR assessment situation is that we have 46 countries done, and 40 member states, and 32 subcountries, and 20 more are in the process, and we will adopt another batch of three tomorrow. That's why I have to leave you already at lunchtime today.

The 32 non-EU countries are listed on this slide. You don't have it in your handout, but you will get a copy. I added this to make it a little bit more clearer.

What you have is the next slide, which is the broad map as it looks from the GBR perspective for the moment. What is apparent is that level three and four is concentrated to Europe. It is the European Union and Eastern Europe.

What is clear is that all these countries have received a lot of imports, and a really big amount of MBM, but also cattle, and most of them have also rather unstable systems, and that means that they would have recycled and probably amplified the agent when it entered.

The point which one should nevertheless make

is that the level of risk is much lower than apparently the U.K., and that all the incident figures that we have so far in the European Union, even on the basis of the massive MBM screening testing that is going on, shows that the order of magnitude is much, much lower than it was in the U.K. in the biggest period.

The same is also for the Eastern European countries. If we look at the time frame of the exports, most of the exports happened in fact in the '90s, and mostly from other BSE infected countries, and the U.K.

And this indicates that in fact the Eastern European countries are very much at the beginning of the BSE epidemic, if an epidemic ever develops. But they are there. If I can go back once more.

The GBR two level, you find in the yellow spread to North America, and then spread to the different continents. The common feature of these countries is that they have some imports of meat-and-bone-meal, or use the customary meals, and flaws and pellets made from meat and offal, and grease, not fit for human consumption.

So looking into these customs figures, we recognize that these countries have received some and

also live cattle, but to a large extent, they have been able to manage the risk of these imports.

However, most of them have unstable systems, and can therefore not be put into category one. In category one then, you find a lot of countries which have very unstable systems.

The reason why they are there is in fact that they have negligible imports, or they have been able to demonstrate that those -- that the number of cattle, for example, entering into their system was negligibly small.

Now, we have finished with that, and now we can go to the next slide. So if you try to estimate the impact, and what does that mean for humans, we should try to estimate the development of the prevalencece.

And as I said, the GBR is not really providing you with qualitative data on this. What it does is that it provides a qualitative estimate of the internal challenge of the imports, and then the qualitative estimate of the stability over time, which means the ability of recycling or not.

And then also the qualitative estimate of what we call the internal challenge, which is a kind of other way of saying prevalence. We avoided using

the word prevalence because it is implying too much a quantitative thing.

So an internal challenge simply means the building up of a pool of infectivity of a domestic heard. It does not provide quantitative estimates of the prevalence, because this would really depend on the quantitative estimates of external challenges to population dynamics, and the relations.

And in effect why we tried this at the beginning, and then the method was developed, and we recognized that the effort would be much-to-much to do this for a large number of countries.

And, two, the data quality is very difficult to reach a level that it makes sense to the developed figures.

As we look at the human exposure risk that the SSC has developed, it provides also an opinion on that. We have a number of factors coming. It is the prevalence of BSE in the live cattle population and the GBR gives you a kind of qualitative idea of that.

Then the prevalence of BSE in the slaughtered cattle. The problem there is that this can be quite different from the prevalence in the live population of cattle. So you have to look into the measures taken at that level, and also the normal

customs.

The age at slaughter is important because of the pathogenesis, which I already mentioned, and the slaughter methods, pithing, is supposed to create a kind of cross-contamination or contamination of the other tissues with SRM, and in particular with brain tissues.

And the use of SRM is an essential key factor, because more than 90 percent of the infectivity is concentrated in those tissues, or at least that is what we are learning. Then the question of the ability of certain processing conditions to reduce infectivity, and that is on your agenda, and you are discussing gelatin, and some new processes there also.

But at least those processes which apparently have a capacity of reducing infectivity by about five logs. And I see that I have to stop, and so the next point anyway is that the imports and exports of food products also influences risk.

And just keep this in mind as you talk about this geographical aspect, because the flows of food products are very, very complex. I will skip the next slide.

And this is taken from the human exposure

according to the SSC just to show you a little bit of the complexity of the passways between the cows and the human consumers, and the central role of SRM.

Again, I am sorry for the time. We have to skip the next one, and so if you would just go through it very quickly. Okay. The European Union BSE risk management was shown by a greater improvement.

At the beginning, it focused on certain elements. So, first import and then vis-a-vis the U.K., and then in '90 the material had to be rendered correctly. But now since 2000 all materials are finally rendered.

In '94, the first mammalian MBM ban was put in place, which is now a total feed ban, and in 2000 finally there is an SRM ban at the EU level. There was something on country level.

And in 2001, a complete surveillance is now in place of all cattle over 30 months, and of risk to populations. To continue, this is just some details. Again, you don't have a copy of it in your handout. You will receive that later.

You just see that in '88 and '89 that there matters of staffing to do, and focusing on the import question, and in '94, the feed bin, and in '97, heat treatment was required for all materials, which took

some time to implement until June 2000.

And since 2000, there is a European-wide SRM ban. On the next slide, SRM being the most important action that you take to put human -- national SRM ban as they came in place, and more or less in line when the countries had their first cases.

You will see that Italy and Spain in '96, only from imported cattle, but not from the domestic cattle; while France and Ireland did a lot in '96 in this field.

In 2000 now we have an European-wide SRM ban which also acts in countries which don't have BSE, and this is the underlying ones. And so I am finished, and I would just like to remind you that you can find all the opinions of the Scientific Steering Committee on the internet at their address, and all of this is in much more detail, and you will find a detailed report for each country. Thank you very much.

CHAIRMAN BOLTON: Thank you, Dr. Kreysa. We have just a few minutes for questions. Does anybody have a question? Quite a few. Dr. Belay.

DR. BELAY: It is my understanding that Category 4 countries include the United Kingdom and Portugal; and that Category 3 includes most other European countries, including France and the Republic

of Ireland.

Now, my question is do you consider countries under the Category 3 to be homogeneous in terms of their BSE risk; and if not, did you try to look at the different countries by different subcategories if you will?

And where would the Republic of Ireland and France specifically would lie in terms of the BSE risk within Category 3? I am interested in the Republic of Ireland and France because this committee specifically looked at these countries during our last meeting.

DR. KREYSA: Well, you are referring back to a discussion which was very intense that we had at the Scientific Steering Committee level in '98 or '99, because obviously this definition of the categories was very, very difficult.

It is very clear that it should be understood that all these four categories apparently lump together quite some different situations in terms of risk.

But the same is true for Category 2 and for Category 3 definitely. The SSC has not really tried to differentiate these different risk levels in much more detail.

The problematic with surveillance data is

very clearly shown now with the upcoming recites from the intensive massive TSE screening recites, which show that the previous purely passive surveillance was not really able to give a correct picture of the situation.

So it is very difficult to quantify within Category 3 the different level of the risk of the different countries because also we don't or we cannot go back in time and prove that level of risk during that period. So for that reason, it was not even tried to really put the countries into different sublevels.

DR. NELSON: I have a question. The question I had was relating the temporality of the risk. In other words, that would relate to the numbers of BSE cattle were identified, and if the risk increased very recently, there would have to be time for the disease to incubate and be shown up in surveillance and the same with humans.

And the concern that I have is that when the problem occurred in the U.K. was there a large export of risk materials to other countries or can we assume that the risk was fairly stable in the group of three countries over time and didn't vary that much?

DR. KREYSA: Well, I think the question of

what happened in the U.K. when BSE appeared is difficult to answer, and a little bit tricky. However, the statistics show that the U.K. changed from a import of MGM to an export in a period of time.

And as they continued to export mammalian MBM until '96, apparently very keenly not to be used for ruminants, and I think that this was even clearly stated in the export permits.

But what happened in the receiving countries was totally a question of the controls in the countries. Since '96, and I think it was March '96, there is an export prohibition from the U.K. of mammalian MBM.

The only MBM exported after that period was poultry, and unfortunately it is included in the same customs categories. So this was one of the problematics that you have looking into those figures.

CHAIRMAN BOLTON: One more question.

DR. EWENSTEIN: Yes. I think we were trying at the last meeting to distinguish between sort of the indigenous risk that might grow up through the cattle from the imported risk directly, say, from the U.K. beef.

And I think that is where France seemed to be a unique situation, or if not unique, then at least

quantitatively different, and so maybe you could comment on that difference of risk.

And now we are talking to the human population that we could assign to the importation of material directly for human consumption, rather than the risk that would then have to sort of grow up through the food chain.

DR. KREYSA: Well, I think that I have to agree with you that the importation of products for dietary consumption is a very important element, and as I mentioned, this is complicating the BSE human exposure risk.

But it is also an element that we have ignored for practical reasons of GBR, because for example if half-carcasses were exported from the U.K. in the late '80s to France, they contained spinal cords, or at least until '99.

And this means that for some time that quite risky material could have been exported for human consumption from those countries. The same thing obviously is with meat products.

Meat products contain the same as mechanically recovered meat. Mechanically recovered meat was made or is made in some countries by using bones from skulls and the vertebra column with or

without including the brain and spinal column.

And it is mixed into a lot of meat products in various more quantities, and these are traded worldwide. So, this is in fact also a source which one has to take into account when looking into the human exposure risk.

CHAIRMAN BOLTON: I would just like to follow up on that exact question. Do you know when mechanically recovered meat was banned from items for human consumption in the U.K., France, and/or the EU at large?

DR. KREYSA: Well, I cannot tell you the dates because I did not look that up. I happen to come across the information that in the U.K. that skull and spiral cord was excluded from mechanically recovered meat in '96.

But other countries continued to produce and use it for quite some time. It is now banned. It is not anymore.

CHAIRMAN BOLTON: Was that EU ban within the last year or so; is that correct? Do you know that perhaps?

DR. KREYSA: I think it was. In fact, the EU ban on the vertebrae column from use in mechanically recovered meat was last year.

DR. FERGUSON: Yes. And I think that was included in the October 2000 SRM ban.

DR. KREYSA: Some countries had included it before, and that is problematic. You have the two different levels which is actually quite complicated, and I didn't look into these in detail. But I could provide you with this information if you want.

CHAIRMAN BOLTON: Yes. I guess the point that I would like to make is that during -- and especially in the U.K. during the peak of the BSE epidemic, mechanically recovered meat was still being incorporated or at least could have been incorporated into food for human consumption.

That clearly presents the greatest risk of exposure of human to BSE.

DR. LURIE: I noticed that at one point that you had on the general slide describing the appropriate levels of precautions that countries at levels one, two, three, and four should be taking.

And I am wondering that even though they were general, if you have any countries that in your mind stick out as being at that particular level, but not taking in a general way the corresponding precautionary actions.

DR. KREYSA: Well, if you want to minimize

the risk that the BSE gets into the chain, you have different intervention points as shown in this GBR model.

And the simple logic is the higher the risk, the more interventions that you should do, and the message from the experience in Europe is very simple. It is not enough to try to control the vicious circle in one place.

You should -- and you probably have to -- act on all possible control points. It is kind of a hazard approach that one should have, and because of this very complex system, it is very difficult to have a hundred percent efficiency of the measures. That is the sad experience which you have to make.

CHAIRMAN BOLTON: Okay. I am afraid at this point that we must move on. Thank you, Dr. Kreysa, again. Our next presentation is by Professor Jean-Hugues Trouvin. It is VCJD and blood risk assessment, an EU policy position. Professor Trouvin.

PROFESSOR TROUVIN: Okay. Thank you, Chairman. It is a pleasure for me to be here to present the new points of view on the geographics of the VCJD and blood products.

And for that, I would like to briefly present the EU analysis, and the situation in the

European Member States, and before touching on the exclusion criteria, and segregation and sanitization issues.

However, before entering the topic of my presentation, I would like to continue on the presentation made by Dr. Kreysa, and insist on a few points on the BSE situation within the European countries. And particularly on the interdiction of animal BSE testing.

Thanks to these tests and based on the most recent figures, it is possible to have an estimate of the global incidence of the BSE. In the EU, incidents calculated for three categories of animals, and these figures lead you to conclude that currently there is no even BSE activity in the EU.

Another point to consider is the introduction of the U.K. cases of BSE reported in Europe since 1998 to March of this year. It is important to mention that cases reported on this slide include those which have been found by testing where the animals are apparently healthy.

From these figures, it is clear that, first, most of the cases have occurred in the U.K., but this is already well known; and, second, that the European countries as such should not be considered as one

single entity.

Moving on to the VCJD question and blood products, and before discussing exclusion types and other strategies, I would like briefly to summarize the main conclusions so far reached by the EU experience.

The conclusions are the results of numerous meetings which have been held at regular intervals in Europe. I have put at the end of this presentation a few slides -- but I will not choose them, of course. Those you have in your handout documents, but to summarize the main dates and documents issued on this question.

Based on all the opinions expressed so far, the risk analysis can be summarized in a few words. First, the situation is different for the sporadic agent and the new variant, of course.

For sporadic, it is possible now to conclude that the risk is remote to absurd in the transmission of sporadic CJD by blood. As such, only exclusion criteria for certain donors should apply, and even it is known that there is no need to recall batches of medical products in case of a donor is found in post-donation to be at risk of CJD.

In contrast, for the variant CJD agent,

there are still many things unknown, and particularly whether or not it is present in blood of the CJD patients.

In addition, it is an emerging agent in the epidemiological data are not sufficient to have a clear view as we have got for the sporadic agent. As such, it is clear that there is a need for adopting precautionary measures.

I would also like to remind the committee that there is a difference in the risk evaluations for plasma-derived medicinal products, which are the products which are discussing today, and the bovine blood products for transfusion.

Indeed, although it is two types of products obtained from the same mechanism, i.e., blood, for plasma derivatives, the manufacturing process has a number of steps that have been now investigated in the ability to remove the TSC agent if present.

And it is available now to compute that tests which are routinely used in the manufacture of these products are produced to remove the agent. Along these steps, to mention the ethanol fractionation, the precipitation steps, or even the leucodepletion.

And these contract with the bovine blood

products from which in their preparation there are no steps identified as either to remove the agent if present in the initial donation.

It is worth noting that at the moment the value of the leucodepletion goes for sedative component and for plasma is still under execution, even if some could consider that at the present time as a precautionary measure there is no reason for not using this product. This is what is done in France, and in the U.K. at the moment.

This slide is also to remind you that the products which are derived from plasma can be used either as active ingredients, such as coagulation or immunoglobulin, but can also be used as excipients, and particularly albumin in a wide range of medicinal products, such as vaccines.

And finally there are also used sometimes as a reagent in the production of biology and biotech products, such as recombinant protein. This is to say that in the biological plasma derived products.

Based on this risk analysis, it is possible to summarize, briefly now, the approach taken in the EU to minimize the potential risk of VCJD transmission by transmitted additives.

First, to mention the U.K. decision to stop

using the U.K. plasma for the manufacture of plasma derivatives. I can tell you that in France they did not go the same way, and maintain the use of the French plasma for fractionation.

Many Member States have also introduced or are introducing an exclusion criteria for donors whose spent time -- 6 months or 12 months -- in the U.K. And as far as leucodepletion is concerned, both the U.K. and France are already commencing this, as have other Member States, after discussing the value of these measures.

And other measures that I would like to mention is the precautionary measure to recall batches in case a donor subsequently gives lots of VCJD, and as you can imagine, France would be at the moment the first EU Member State to actually apply this measure one way or another.

And finally all the measures and recommendations are essentially aimed at diminishing the side of the population exposed to blood and blood products.

Briefly, there are other measures which can be mentioned as having been adopted by some EU Member States and this potentially to mention the exclusion of donors with neurosurgery, but also permanent

deferral for donors who have previously been transfused to remit the diminution of the potential agent.

Now, going to the question of exclusion criteria, I would like first to remind you of the risk factors so far identified. The main risk factors seems to be the residence, time, and time spent in the U.K. as clearly indicated by the hundred of cases reported in the U.K.

However, we have also to take into consideration the risk factor for a donor of being exposed to the BSE indeed only count three, even without traveling to the U.K.

There are three cases in France, and it is clearly traced the endogenous risk, which is essentially depending upon two factors. First, the BSE incidents within the country, as well as the delivery of imported BSE infected material from the U.K. in 1990-1996.

This is to say clearly that EU countries have a different level of risk, and that we have a wide spectrum, starting from the most risk situation within the U.K., and ending very lightly with Finland, for example.

Again, we are still of the notion that

Europe should not be considered as one entity. As an example, in France, it has been exclamated that the risk is 1/20th of the risk exposure in the U.K.

And we estimate the potential date of two figures. The importation rate of future MBM and entering the food chain in France in the period at risk, and the three percent related figures in VCJD cases in France compared to the U.K.

And these two figures are very close, and we see certainly incidents. However, these two figures are a clear and good indication of the BSE exposure risk in France are endogenous or imported.

As such, France should be considered as the worst European case after the U.K., and it is very unlikely that any of the other EU Member States will ever catch up with the U.K. or French situation.

And with discussing the scientific basis for deciding exclusion criteria, I would now like to discuss the possible frequency of further exclusion measures are settled.

First, we have to consider for plasma derivatives that this is a global market situation. Indeed, for U.S. plasma first, as you know, commercial producers are working on a global scale using both U.S. and EU plasma.

And even if the destination of the resident products are different, this is a global market. It is also important to mention that since 1998, when the U.K. decided to stop fractionation of their plasma, they have been using U.S. plasma in such a quantity that when in France, they attempted to find potential sources of plasma outside France and the EU.

It has been impossible and the plasma market was already reserved.

Now, in the European picture, we have almost the same picture. Indeed, the commercial producers are using plasma collected essentially in Germany, Austria, and Sweden.

And as the plasma is delivered, the plasma is collected usually by the National Red Cross organization, and sales to produce plasma derivative medicinal products which are used domestically, but also certain diseased products enter the global worldwide market.

And I think with those elements in mind, it is very easy now to see the foreseeable frequency of new stringent exclusion criteria which could be taken at the U.S. level.

There will be first a further loss of U.S. donors, and then the diminution in plasma

availability. And an increased demand for U.S. plasma and for the finished product because of a passage of recent induced by the exclusion decision.

And there could even be the case where commercial producers could decide to no longer use the EU plasma anymore. This is to say that the consequences of an exclusion measure of not only to be considered at the U.S. level, but also under a worldwide scale.

Another alternative or proposed measure could be the segregation of manufacturing line. At the moment, the situation is that commercial producers are making use of the same manufacturing line to fractionate U.S. and/or EU plasma at least in the EU manufacturing sites.

However, it should be acknowledged that in these manufacturing facilities the EU plasma has the same exclusion criteria as the U.S. plasma at the moment.

However, what would occur if the EU plasma, due to new exclusion criteria applicable for the U.S. plasma is no longer or can no longer co-exist with the U.S. plasma on the same manufacturing line.

The imposed segregation line will impact on plasma availability and it will take a substantial

period of time to establish a separate line, and eventually even to close facilities for implementing this segregation.

There will be the question of what to do with batches produced and eventually to evolve the segregation issue, and producers may even decide not to use the EU plasma, and we are back to the situation forcing segregation.

And finally, but not too forget it, the segregation creates a loss of flexibility to move to alternative facilities. The last point just before concluding deals with the sanitation procedure, which has to be envisaged as an alternative to line segregation.

However, depending on the type of sanitation procedure to be put in place, this could also impact on the time scale of correction, and therefore diminution of the global and world production capacities.

All these elements have to be taken into consideration before making any decision. The respective value of each individual measure has to be technically evaluated.

In conclusion, I would first like to stress again that for blood or blood products that a local

policy will have local impacts for plasma derivatives, and it is clear that the impacts of any proposed intervention have to be initiated globally in a worldwide approach.

And with the exclusion of donors who spent time in Europe, the impact on the blood supply is largely dependent on the option chosen. As long as the option maintain both the EU and U.S. plasma are the same or very similarly level of requirements, the global impact on plasma supply would be affordable.

With regards to segregation, just to remind that segregation would take considerable time to put in place. The U.K. experience which has been reported in front of this committee two years ago should be considered in this respect.

The improvement of sanitation procedures may be seen as a possible alternative to line segregation, and should be technically investigated. And finally, as a general comment, Chairman, I would like to stress the need to balance any precautionary measure against the real risk of supply shortage in plasma products. Thank you.

CHAIRMAN BOLTON: Thank you, Professor Trouvin. Do we have questions from the committee?

DR. EWENSTEIN: You seem to be making the

same case that we made last time to look at France differently than perhaps the rest of Europe. How does that translate into your own recommendations for French donors versus the rest of Europe?

PROFESSOR TROUVIN: If you -- the French case as apart from the rest of Europe -- at the moment, and maybe as we knew, and maybe you knew that in Europe the French plasma is essentially used for fractionation and for internal and domestic use in France.

There is very few plasma used in the European plasma collections, and the derivatives that are derived from the French plasma. So this means that it is a very internal market for France.

So even if there is a further exclusion criteria for those donors who spent time in France, and restriction for French donors, the impact on the global availability would be very little.

CHAIRMAN BOLTON: Okay. Thank you, Professor Trouvin. Our next presentation will be by Dr. Christl Donnelly, and it is the mathematical modeling of potential human BSE exposures in various BSE countries. Dr. Donnelly.

DR. DONNELLY: Thank you for inviting me back. I first spoke to this committee -- well, the

one other time, two years ago when the consideration was focused on the U.K.

And I pointed out that in some ways I had the easiest job of anybody advising you, because there was a great deal of data on BSE and the U.K. We knew very precisely what was going on.

But you had to consider what was going on. First, the potential risk of variant CJD infection from food, and then furthermore what that might pose as a blood risk.

When we moved to BSE in Europe, as you will see in the course of this presentation, things are very different. There is the BSE you see and the BSE you don't. The BSE you see comes in two forms; traditionally reported clinical cases, and these reporting varied through and from country to country.

It has been the case of every BSE epidemic that has been -- every country's BSE epidemic that has been analyzed in detail -- Great Britain, Northern Ireland, France, Portugal, Switzerland, all of those countries that have had substantial BSE epidemics, when you actually look at the data in detail, the ages of animals infected, you can find evidence that cases were under-reported to begin with.

Now the difficulty in switching from

analyzing those countries to countries where you only have a couple of cases is impossible to prove just looking at the fact that you have had two cases in the country, and whether you have excellent surveillance, and have picked up the only two cases that have happened.

Or whether you have poor surveillance, and you have only picked up two out of "N" and where "N" could conceivably be quite large. But more recently and starting at the beginning of this year, there has been the requirement across the EU, not for Britain, and as I will explain later, but for other countries across the EU, to test using a test for animals slaughtered for consumption over 30 months of age.

And this provides primarily not consumer protection, although it was misinterpreted initially, because the test won't necessarily pick up all infected animals.

But it gives from the point of view of risk assessment an objective additional piece of information where we can actually then distinguish between those countries that have surveillance, and where they are picking up everything and are just low cases.

Or where they might not be picking up the

cases. So we can compare these two. But it is important to realize the risk to humans comes from BSE you don't see.

Those animals that are picked up as reported confirmed cases are not then eaten by anyone. Also, those animals that are tested over 30 months that are tested and come out positive aren't eaten.

So it is the other infected animals that weren't picked up and either of these methods that were consumed and therefore pose risk to humans from direct transmission from BSE.

The ratio of infected -- of original infections to clinical cases, even with a completely reported situation, is about 5 to 1. And that is because the incubation period of BSE is so long, about five years on average, compared to the average life span of cattle.

And most of those animals will be slaughtered early in the incubation period, but still it means that in the UK we estimated on the order of three-quarters of a million infected animals were eaten over the course of the epidemic, compared to the 178,000 clinical cases that have been reported so far.

What I was originally going to concentrate on in this talk was on that calculation analyses that

the technique originally designed for the analysis of age data that our group developed in 1996 for the analysis of the U.K. BSE epidemic.

Since it was used to analyzed data in Portugal, and you can see here that it was originally analyzed in 1998, and we were able to estimate using various assumptions under-reporting what the infections were through time.

You see the infection incident on the top graph on the right by birth cohort, which shows that it was variable. The blue is, if I assume no under-reporting, and all cases were reported fully.

The red is if I allow for under-reporting, because the age profile of the cases that you see gives you some indication of what reporting patterns were through time. And that leaves at the bottom as you can see projections of future cases. Next slide, please.

More recently in France, I published an analysis last December looking at the epidemic in France, and there was particular concern because the year 2000 had the highest number of cases so far.

Now, what you see in the epidemic in the U.K., both in Great Britain and in Northern Ireland separately, is that these epidemics peaked in terms of

the number of cases back in the early '90s, and the case numbers are going down reassuringly.

The problem is that when you look at other countries, you find in some cases that case numbers are still going up. But the difficult balance is what you want to know is what the pattern of clinical cases was, because that gives you some idea of what the pattern of exposure was.

But what you see is reported clinical cases. So you could have reporting going up, and clinical cases going down, and it still looks like the risk is going up.

But now because of this additional information we have across Europe, where it was actually looked beyond the clinical case data, and look at the actual testing data.

This shows the estimates allowing for reporting and under-reporting in this graph on the right. In the red, it shows my estimates if I allow for under-reporting; and in the light blue, if I don't allow for under-reporting.

And you can see that you get varied different estimates. As I said, allowing for under-reporting substantially improves the fit. You can find significant, very significant statistical

evidence of under-reporting through time.

This, combined with more recently -- earlier this year an analysis of the Republic of Ireland of what got a lot of press interest was the conclusion that because of the 30 month ban in Britain, and I think this is the key thing that was chosen, that 1996 was chosen as the cutoff for Britain in the ban that was selected two years ago, is because in 1996, a whole lot of things happened with the identification of variant CJD.

Two very critical things happened; stopping the animal epidemic, in terms of primary infections in huge clampdowns and additional regulations on feed, and including monitoring of feed.

And there are various enforcement documents that you can find on the web that show testing that goes on in various speed lots to look for both on material or mammal material in any bovine feed.

And also the most direct thing to prevent additional human exposure was this ban on animals over 30 months being slaughtered for consumption. And that has been in force from 1996 and continues to be.

This did not take place throughout Europe. It was only in the U.K., and as a result, with the increasing numbers that we are seeing in France and

Ireland, you could actually find that in the year 2000 there were more late stage infected animals, those animals within 12 months of clinical onset.

And which have been found in various tests to be potentially the most infectious to mice in tests, and that there were more slaughtered for consumption in France and in Ireland than in the U.K.

I would argue that this is not the key relevance to you, because you are worried about the main bulk of infections, and even these were with relatively small numbers.

The reason that the U.K. number by comparison is so small is because of the 30 month age ban. But compared to the 750,000 infested animals consumed over the course of the British epidemic, what is going on in terms of these relatively small distinctions is not key.

The key thing is in looking at the overall course of the BSE cases in the BSE epidemic, what that means in terms of variant CJD risk. You see here in purple the things that we have information on, the BSE cases and the variant CJD cases, and in between are all of those boxes for things that we don't know very well.

How infection was transmitted, and how

infectious it is, and what the human incubation period is. And we found by our analyses in the U.K. that there is a wide range of scenarios that are consistent with the BSE cases and exposure that we have seen, and the number of variant CJD cases, which is roughly about a hundred right now in the U.K.

So this could range in terms of future epidemic size from very small epidemics and we would see relatively few additional cases if the incubation period is relatively small, to considerably more cases, over a hundred-thousand, even in the 40 percent of people that have a specific genotype.

It is the one that has been shown to be susceptible. We don't know yet about the 60 percent of other people, and whether they are less susceptible or simply have longer incubation periods.

The difficulty is, of course, that not only do you have all that uncertainty, but you are adding the additional uncertainty of when we have done those analyses we have assumed that all infections come from feed, or from food, to humans.

And that in terms of order of magnitude, the right thing to do for this sort of assessment now. But since there is the possibility of blood borne infections, that adds another layer of uncertainty,

and means that you are really dealing with something where you don't have epidemiological data.

Even over the course of the whole epidemic, if we look back on this in 20 years time, we won't actually know which people for the most part, we won't know for the most part which people were infected by blood and which from food.

So I think the key thing that I am going to focus on then is this European testing program. There are limitations though. I don't actually know the ages of animals that were tested specifically, and the ages of those that were positive.

There will be age facts both in terms of animals born at a particular time might be more likely to be infected, and also the fact that this sort of testing is almost certainly picking up only very late stage infections, which means that even if they were testing animals under 30 months, they would probably pick up few of those animals that are infected. So there is that caveat.

But within those limitations I think we can see some very interesting results. This shows -- and I will show you graphically the conclusion of this, and so don't worry about all the specific numbers.

These are European countries, EU countries,

not including the U.K., and this requirement of testing of all animals over 30 months slaughtered for consumption doesn't apply to the U.K. because those animals slaughtered over 30 months aren't for consumption.

So I am just comparing these countries, and also because Switzerland is not in the EU, and it does not have comparable data, and so it is not shown here.

This shows the results, which show that there were 76 infections found in the nearly 1.8 million healthy adult animals that were tested across the EU. But it is interesting to look at where these actual animals are found.

I will mention Portugal specifically a bit later, which has found no infections, but does have 37 results pending, which I am not exactly sure what that means. Next slide, please.

I think it is important to look at the variable amount of testing effort before we actually look at it, because if you are doing less testing, then you are less likely to find positives. So you should take that into account.

And you see that it varies actually quite a bit, and Sweden had no tests at all. But you find that Germany has had a huge number of tests. This is

healthy tested cattle per million adult cattle in population.

And so it should be comparable across countries. It should be independent of actual size. You see that Portugal surprisingly for a country that has relatively such a high risk is doing relatively little testing.

But other countries are doing considerable amounts of testing, and these results have come through. Next slide, please.

Presenting the results here in two ways, showing the difference in ordering. Here I have shown the prevalence expressed in positive per 10,000 healthy animals tested, in terms of the estimated prevalence.

And you see that Spain is the highest, 22 positive tests out of the animals that were tested, and that drops off, and you see that positives were found in Italy, Belgium, France, Germany, The Netherlands, and the Republic of Ireland.

I then have shown you for those countries that have found zero infections, and in each case the 95 percent confidence interval, which we statisticians like. And that shows you that if you found no cases, how certain are you of what the prevalence is.

And you see like in cases in Finland, and Portugal, and Greece, and Luxembourg, the testing numbers are so low that you could have still a very wide range of possible incident levels.

So then in the next slide, we will look at the possible potential risk for prevalence, and you see that it is still possible that the four countries -- Finland, Portugal, Greece, and Luxembourg -- could have potentially higher prevalence than Spain, because their testing is such that they can't rule that out.

But I think that you need to keep these two things in mind. How much testing has gone on, and what prevalence has actually been found. But I think one of the key results from here is that you can see by looking at this that Spain has significantly more positive tests coming out than France does.

And Portugal still has or is in the range of that confidence interval, and I showed 32, 26, and 12, and that is the upper limit of the confidence intervals for the countries of Finland, Portugal, and Greece. So they really are hugely variable. Next slide, please.

Then you think, okay, let's compare what has been found in terms of the testing results with what had been reported in clinical cases. And what I have

done is shown you the reported clinical cases that were confirmed before 2001.

Because it has been pointed out that France had more cases in 2000 than in previous years, and Portugal's big leap in case numbers was in 1998 and so on. But you are finding that some countries are now reporting clinical cases that hardly had ever had them before, Spain being one of those.

In the past, Spain had two cases that were showing up in the end of 2000, and there are now reports of clinical cases in Spain, as well as the 22 positives that were shown up through testing.

So I think one of the lessons from this is doing testing of asymptomatic animals can have a good effect on your reporting levels of clinical cases. But what it does show is that there is not a good concordance between the relative prevalences found in terms of testing, and not found in clinical cases.

So I think it would be very difficult for you to actually pin all your hopes on looking at relative risks in terms of just those reported clinical cases, because it is a difficult balance between what cases occur and what are actually reported. Next slide, please.

And finally I have shown you still the same

reported incidents, in terms of the number of cases, but compared to the reported clinical cases per millions of adult cattle, because I think it is important when you are actually looking at this to take into account that two BSE cases in a country with a much larger cattle population does per State pose a lower risk, or per unit of MBM.

And again you see that Portugal as being the highest, and I think that's why it was put in this top category with the U.K., and to put these numbers in perspective though if you were looking at reported clinical cases per million adult cattle in the U.K., that would be on the order of 18,000.

So these are still considerably lower risks, and I should point out that I sort of categorize things in terms of the color of relatively high, medium, and lower risks.

These were purely -- I was just trying to give you distinctions looking at them. I am not in any means categorizing them on the basis of what you might want to do in terms of precautions, but just showing you to compare.

And the other one that I should point out is Italy, which had no clinical cases reported before 2001, has the second highest prevalence in adult

healthy cattle tested. So it has been extremely difficult in comparing those two things. And the next slide, please.

If you were looking in 1996, only those three countries -- Portugal, the Republic of Ireland, and France -- had had clinical cases by then. So things are changing all the time, but I think it is this testing that doesn't help you realize in non-EU countries.

But I think that the testing program that has gone on in the EU will show increasingly more information that you can actually use, and that you don't rely on countries reporting systems and the debate that surrounds that. Next slide.

And the way to learn more about this is that the British epidemic is described in what was the Ministry of Agriculture for Fisheries and Food, and what we now call DAFRA, which has a website.

And there is information on worldwide BSE from the International Organization for Animal Health, and there is access to this EU cattle testing data also on the web through the U.K. Food Standards Agency, and through the EU. Next slide, please.

And there is additional publications, and I am happy to send people by E-mail a list of more

publications, and finally I should thank my colleagues that have worked on this with me over the past 5 years. Thank you.

CHAIRMAN BOLTON: Thank you, Dr. Donnelly. Questions? A few maybe, or perhaps none.

DR. DE ARMOND: I have just some simple questions. Can the clinical diagnosis of BSE be confused with any other disorders? Are we really certain of those numbers?

DR. DONNELLY: Oh, I think there are quite a few -- well, it is difficult for me to answer that. It has varied over time in the U.K. In the U.K., there is quite a few animals that are put forward by vets and farmers that when tested histologically are found ont to have BSE.

So certainly even in the U.K., where vets should be relatively familiar with it. But people are encouraged and actually get greater compensation for animals that are slaughtered and found BSE negative, and even for the BSE suspects themselves, they are paid to encourage reporting.

It is probably better maybe for one of the vets to comment on that, on the histologically background, but there certainly are those epidemiological evidence that it is difficult.

But that is sort of distinguishing what you have identified as suspect. Actually, what we are worrying about here is just not realizing that you should call the vet in at all.

And certainly from the video that I have seen, if you allow an animal to go to late stage disease, I think that any farmer should see that something has gone wrong with it.

And it could be that milk yield goes down, because the animal is not milking well, and so it gets sent to slaughter before it is actually realized that something is more fundamentally wrong, and it is difficult to rule that out.

DR. DE ARMOND: The other question has to do with testing of normal animals without clinical disease, and what kind of testing was that, and that is in a lot of animals, close to a million animals.

DR. DONNELLY: Yes.

DR. DE ARMOND: So, how was that done?

DR. DONNELLY: The so-called rapid test. I am not actually aware of the -- and some other people would be in a better position to discuss that, but my understanding is that it is a test where you really only pick up late stage animals.

But the difficulty is that these people

aren't aware of how early in the incubation period it will pick them up.

CHAIRMAN BOLTON: Dr. Cliver and then Dr. Piccardo.

DR. CLIVER: The signal to noise ratio about BSE tracking in the U.K. has been perturbed by the foot-and-mouth disease outbreak, and along the way we see some concerns about FMD animals that were put down, and then buried somewhere there was ground water intrusion and so on.

I am wondering if anything is being done in the U.K. to try and get a handle on how stable and transmissible BSE prions may be via ground water or surface water, or alternate routes of transmission than the ones that we are already considering?

DR. DONNELLY: There is. The only cattle that have been buried as a result of foot-and-mouth disposal have been animals under 30 months of age, and the TSEAC group in the U.K. spent a lot of time considering whether to allow that.

But the scale of the foot and mouth slaughtering and disposal problem was such that that choice was made. There were details and sort of environmental assessments of the areas that were chosen, and I believe that is being studied.

But it would be best for this group to contact TSEAC directly on what the actual details are that are going on. In terms of actual surveillance of BSE, I don't think the foot-and-mouth epidemic will have any long term consequences on that, because as well as delaying that from getting on to the farms, it was actually delaying animals getting slaughtered, and in terms of routine slaughtering as well.

So I doubt that that will actually affect the clinical cases that we see reported.

CHAIRMAN BOLTON: Dr.Piccardo.

DR. PICCARDO: Will governments in the European Union provide compensation for reporting or is there a discrepancy among different governments?

DR. DONNELLY: My understanding is that all European countries would provide compensation for BSE cases. It also is the case that outside the U.K. the whole herd is slaughtered.

Oh, it has been changed, but this has historically been the case, that the whole herd was slaughtered, which would have positive benefits from a human health point of view; that if you got a clustering of cases, that would ostensibly reduce the number of infections of animals that might slaughtered while infected out of that heard.

But it does mean that there have actually been cases prosecuted in the Republic of Ireland, and I don't know of elsewhere, but where people were actually trying to import a BSE infected animal into their herd so that they could get out of farming.

But I think that for the most part that the whole herd slaughter policy could be seen as a possible disincentive to report a single case if you wanted to continue to farm.

DR. PICCARDO: I am suspicious about the situation in Portugal, because it shows that the amount of clinical cases reported and the amount or the discrepancy between the number of clinical cases and false-positive cases.

DR. DONNELLY: Yes, I was quite surprised as well that they had zero positive tests, but one of the things that you do see is that they have done a lot less testing than you would expect compared to other countries, and they are the only country that lists pending results.

So if in the worst case scenario all those 37 were positive, they would be at the top of the list in terms of prevalence. I did look back though at previous months to see what the pending results were, and there have been pending results throughout the

case, but you would certainly want to see how those are getting resolve.

Did the results that are listed as pending now, are those later going in as negatives, and you get other ones showing up as pending; or is it just an increasing class. But that could be investigated.

CHAIRMAN BOLTON: Dr. Epstein.

DR. EPSTEIN: You mentioned approximately three-quarters of a million infected animals may have been consumed in the U.K. in the epidemic period. Are there comparable figures for other countries that you have been able to estimate, because what we are mostly concerned about the cumulative human risk, country by country.

DR. DONNELLY: Well, it is extremely difficult because of this problem of under-reporting. It is certainly the case that you could have tens of thousands of infected animals eaten in countries like Portugal, Ireland, and even France, depending on what you submit under your reporting, and Switzerland.

But the difficulty is of course if I looked at France a year ago, and before we had actually seen the 2000 case data, I would have given you a very different picture for France.

So I think that actually the estimates will

be much better in a year's time when we have actually had more data from this testing result, because we can only say, well, when you do this in an assessment for under-reporting, you have to assume that at some point that under-reporting went up to a maximum level of, say, a hundred percent.

And if you assumed that reporting improved up to that level this year, looking at 2000 as opposed to next year, you would get a very different picture for Spain, for example. So it is very difficult to be precise at this moment.

DR. DAVEY: One more question. Well --

DR. BELAY: Dr. Donnelly, there are still some BSE cases reported in the United Kingdom among cattle born after 1996, despite the fact that the control measures were rigorous after 1996. What are those cases attributed to?

DR. DONNELLY: There have only been -- I think it is either 2 or 3 cases that have been born since mid-1996 that have come out as clinical cases. One of the things that our group did -- and we were involved in two different assessments of data relating to maternal transmission of BSE.

That is the maternal cohort study, which looked at animals to BSE infected dams and a matched

animal in the same herd, and that showed an increased risk of BSE in the off-spring.

But since that was ambiguous, it could have been genetic. We also looked at the database and found more dam calf pairs of BSE cases than you would expect by chance in those animals that were the last born calf, and we would suggest that it was maternal transmission.

We then looked at how many cases of BSE we would expect in animals born after 1996 due to maternal transmission alone, and found that this is in excess of what we are seeing now if you assume 10 percent maternal transmission in the last six months of the incubation period.

That said, it is my understanding that one of these animals that is a BSE case that has been found, its mother is still alive, and is apparently not affected by BSE.

And it also has off-spring and it has siblings that are also not affected by BSE. So it is very difficult to figure out how this animal could potentially have been infected unless it was through a non-maternal means, because all the evidence that we found is that it is only in the very late stage of infection that is maternally infectious.

So there is that one animal, but it is uncertain. But so far in monitoring it, we have seen fewer cases than we would expect through maternal transmission in these animals born after the middle of '96.

CHAIRMAN BOLTON: Okay. Thank you, Dr. Donnelly. I think it is best that we move on as we are rapidly running behind schedule. Our next presentation will be by Dr. Antonio Giulivi, and it is entitled, "BSE Exposure, Risk Reduction, and Projected Effects on Blood supply." Dr. Giulivi.

DR. GIULIVI: Thank you. Mr. Chairman, and Ladies and Gentlemen, what I will be doing is presenting a risk assessment that Canada has done, and you have to understand the way we work in Canada.

The department that I head up is a public health department. We work with industry, and we work with the blood centers and so on, and we also give information and assessment, risk assessments, to the regulators, a different department in Canada, and we are completely separate.

And we are able to interact freely with different consumers and so on, and so we usually do risk assessments and we also suggest to the regulators what we think in public health will happen.

This is a step that has been three years now and it has been working well. It is experimental, and this is the way that Health Canada is working, and it is working quite well.

So what we did is that the regulatory people asked us to look at again the situation of all of Europe and BSE, and should there be deferrals for donors in blood for Canada for travelers that went to Europe.

And we constantly do this every 2 to 3 months, and so it is an open book, and we just don't shut the book. We keep on doing that. The other thing that you will see, and which is the most important slide at the end, is the blood supply, and the amount of supply in the hostel.

We have seven hostels that we fund to look at what happens if the blood is not there. The other thing is that at the end of my presentation the CBS is going to present four slides on how they got to their risk assessment and how they got to their donor assessment. It is quite important and I would like for them to present that data.

So we took all of this into consideration, the past and the present, and we took into consideration when things started to happen, and when

it was discovered, the theoretical risk,a nd look at the literature.

We have our own experiments that we are doing with Health Canada with animals and so on about transmission, and we are funding some elsewhere. Then the story of what happens in France with the three cases, and then animal studies that may support the transmission of blood, and I can actually say may. The next slide.

We looked at the total cases of VCJD in the U.K. and France., and we knew at that time while we were doing this that we knew about the case already of Hong Kong. The annual reporting of the BSE beef during this time -- and this was very hard to find -- reporting the number of cases of BSE in Europe.

And then we predicted the BSE. because what we are looking at is -- the first question is the BSE of that country appearing in our country, is that the same risk as the U.K. that happened 10 years ago.

What is the magic number of how many cases you need to consider that country high. That was the question that the regulatory asked us. So we had to do all these analyses for every country, which I am going to go very fast through it.

The bottom line to it is that it is our

conclusion that you need at least 1 in 700 animals coming down with BSE before you can consider that country the same risk as the U.K., and that was our conclusion.

We looked at the emergence of the BSE, and the disease probability presenting earlier, and how it develops. You heard this before with Donnelly, and the exposure. We looked at the bans that took place in different countries, and especially with the U.K., and then all bans that took place in different countries, which was very hard to find.

We looked at the human exposures that may have started in the U.K., and we really took this into consideration. This was the major risk for us, the mechanically recovered meats.

We looked at how the graph was going on reported cases of variant CJD, and Canada is part of the U.K. system, a European system of reporting variant CJD and CJD, and we are very active in that.

We get a lot of information from a lot of countries, and you can see that we are predicting that this would be around 30 to 40 this year for the U.K. So there is an increase, and that made us rethink maybe our policy for blood has to be changed because of that increase in the U.K. The next slide.

The information that is not available in the incubation period, and we assumed it was 20 years or better. The minimal dose we still don't know. The age distribution and slaughter, and the dietary habits between U.K., France, and other European countries. Next slide.

We looked at the probable source, which again we did the mechanical, and that's where we really pointed to, and the prevalence of the countries that it would transmit to, the animal or cow, and the food imports. Next slide.

Now you are going to see a lot of graphs on the prediction of the countries that we looked at, the BSE countries that will all happen the next year or the year after, and so on.

These are predictions that are done, and they could be off, but for us to sort of give a value to work with. Next slide. We looked at the categories, and we took all the information from Europe. Next slide.

And we looked at how the cases of BSE was appearing in certain hard to predict countries. Next slide. And then we looked at the annual imports of U.K. beef by the country, by certain countries, and we see some of that information through the U.K., and

some through WHO, and some through contracts, and through official contracts with governments. Next slide.

And this is what we got. The increase you can see keeps going down, and then the increase of all other countries, but when we predict and predict high, you will see that it doesn't go as high as a thousand per month, and that is what is important.

So in public health, which is my department, we said that the public health, that really what you have to look at is U.K. and France. The other countries are going up, but they are not hitting the level of what happened in the U.K. Next slide. And you can see that it is going and increasing. Next slide.

And I am going to show you some graphs that it was hard to predict these numbers, because of the confidence intervals are all over the place, but this is what you have to deal with when you deal with these models.

So this is for Belgium and for France, and it was easier, because it is a tighter fit. Next slide. For Germany, there is a big variance there. Next slide. And for The Netherlands it is the same big variance. Next slide.